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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/017,472	CHADA ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,7-12,14,18-23,25,33-43 and 75-79* is/are pending in the application.

4a) Of the above claim(s) *2* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7-12,14,18-23,25,33-43 and 75-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/19/07 has been entered.

The amendment, and remarks filed 12/19/07 are acknowledged. Claims 13, 15-17, 32, 69-74 have been canceled. Claims 1, 75, 76 have been amended. Claim 79 is newly submitted. Claims 1, 2, 4, 7-12, 14, 18-23, 25, 33-43, 75-79 are pending.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 12/19/07 response would be addressed to the extent that they apply to current rejection.

Election/Restrictions

The claims under examination are subject to an election of invention and species requirement; see the office action mailed on 2/24/03. In the response received from the applicant dated 3/17/03 and 7/7/03, the applicant elected without traverse of group I, drawn to a method of using a mda-7 nucleic acid(s), and the species drawn to treating an angiogenesis-dependent cancer, using the fragment 182-206 of SEQ ID No: 2, and

adenoviral vector for examination on the merits. Applicant later filed a petition requesting rejoining of non-elected species, which was granted-in-part. Applicant now amended claims so that the claims drawn to rejoined species are canceled. Currently, only claims 4, 35, 77, 78 are limited to the elected species (angiogenesis-dependent cancer) concerning treating a genus of angiogenesis related diseases, using a nucleic acid for treatment.

It is noted upon the amendment dated February 28, 2007, claim 2 no longer reads on the elected species, as it now directed to a disease other than cancer, and hence is withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim.

Claims 1, 4, 7-12, 14, 18-23, 25, 33-43, 75-79 are under current examination, and have been examined **only** to the extent that they read on treating angiogenesis-dependent cancer using a nucleic acid expressing human MDA-7.

Specification

The amendment to Specification filed on February 2007 requesting change of inventorship has been granted, and the record will be corrected to delete Elizabeth Grimm as an inventor. As a result, the rejections under ***35 USC § 102*** are withdrawn.

Claim Objections

Claim 77 is objected to because of the following informalities: it depends from a canceled claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 7-12, 14, 18-23, 25, 33-35, 75-79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 has been amended to recite "providing to endothelial cells in the patient by local injection an effective amount of ...". Since endothelial cells are present in the inner lining of blood vessels and any membrane of the body, they are everywhere in the body of a subject, it is not clear what location is considered "local injection", and hence, the metes and bounds of the claims are uncertain.

Claims 75 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons of record and following.

Claims 75 recite the limitation "viral particles". There is insufficient antecedent basis for this limitation in the claim.

In the remarks, Applicants insists that the skilled artisan would understand that the number of viral particles recited in claims 75 and 76 refer to the amount of viral vector [of claim 8] that is administered to a patient.

In response, vector and particle are two different words in English language, and encompass different scopes, a viral vector may encompass a viral particle, but it also encompasses a naked DNA, for example. The specification fails to redefine the two phases as being equal alternatives. While it is clear to recite "viral particles of the viral vecotor, it lacks antecedent basis when reciting "viral particle" alone as does claim 75. Further, claim 9 depends from claim 8 and is directed to administer the viral vector at 10^3-10^{13}, while claim 75, also depends from claim 8 and recites administering viral particles at 10^{10} to 10^{11}. It is unclear whether the substance administered in the two claims are the same or different, and whether or how the dosing regimen for claim 9 and claim 75 comparable. Thus the metes and bounds of the claims are uncertain.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 7-12, 14, 18-23, 25, 33-43, 75-79 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *intratumora* administration/or administration at a site near or local to the tumor, of a nucleic acid expressing a full length MDA-7 polypeptide or secreted form of MDA-7 (lacking a secretion signal, i.e. the fragment 49-206 of SEQ ID No: 2) for treating

angiogenesis-dependent cancer, does not reasonably provide enablement for distal or systemic administration for treating angiogenesis-dependent tumor, for reasons of record.

Claim 1 has been amended to recite "providing to endothelial cells in the patient by local injection an effective amount of ...". This appears to be an effort to address the issue concerning the route of delivering nucleic acids. However, given the broadest reasonable interpretation, instant claims as written reads on delivering the MDA-7 anywhere where there are endothelial cells, not limited to locally in the cancer supplying vascular endothelial cells. Moreover, claims 18, 19, 36 still read on systemic or distal adminstration, and hence for reasons of record, the rejection stands.

Claims 1, 4, 7-12, 14, 18-23, 25, 33-43, 75-79 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *intratumora* administration/or administration at a site near or local to the tumor, of a nucleic acid expressing MDA-7 polypeptide for treating angiogenesis-dependent cancer, does not reasonably provide enablement for other means of administering to endothelial cells.

The amended claim 1 read on "providing to endothelial cells in the patient by local injection an effective amount of a nucleic acid expressing the human MDA-7". The applicant points to text in pages 11 and 23 as support.

The relevant text in page 11 reads:

> In other embodiments, a method of inhibiting endothelial cell differentiation comprising administering to an endothelial cell a nucleic acid molecule encoding human

> MDA-7 protein under the control of a promoter operable in eukaryotic cells is described. Alternatively, the mda-7 expression vector can be administered to tumor cells or at a site near or local to a tumor, thereby causing the release of MDA-7 protein. The MDA-7 protein will bind to endothelial cells and inhibit angiongenesis.

Keep in mind, the claimed invention broadly encompasses treating any endothelial cell growth and differentiation related abnormality, hence, the first half of the paragraph generally refers to administering the therapeutic molecule to endothelial cells; whereas the second half of the paragraph addresses specifically about treating cancer, wherein the expression vector may be administered to tumor cells or proximity of tumor, and the MDA-7 will bind to tumor endothelial cells to inhibit angiogenesis. In working examples, the applicant used intratumoral injection as means of delivering MDA-7 to endothelial cells (e.g. line 4, page 90). The specification fails to teach any other means of delivering MDA-7 to endothelial cells, which would effectively inhibit tumor angiogenesis. Thus, the specification fails to support what is now claimed.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 7, 8, 10-12, 14, 25, 33-36, 42, 43, 77-79 are newly rejected under 35 U.S.C. 103(a) as being obvious over *Fisher* (US 6,355,622), in view of *Folkman* (Seminars in Cancer Biol 1992;3:65-71).

Fisher teaches a method of inhibiting cancer in a subject comprising intratumoral administering, to nude mice bearing human cervical carcinoma cells, replication deficient adenoviral vector encoding the full length mda-7 protein (e.g. column 6, lines 27-65), wherein the full length mda-7 is a polypeptide comprises amino acid 1-206 of SEQ ID No: 2; wherein the administration regimen was three times a week for 4 weeks. Fisher then meansures the tumor volumes twice to three times weekly with a caliper to determine the cancer inhibiting effect of MDA-7 (column 14, lines 49-56). *Fisher* reports the growth of well-established tumors were inhibited in the mda-7 treated mice compared to the control group (column 14, lines 35-67), wherein the expression of mda-7 was driven by a CMV promoter (column 13, line 56). *Fisher* also teaches that the nucleic acid could be embedded in liposome and introduced into cells (column 3, line 67, lipid composition). *Fisher* also tested anti-cancer effects of mda-7 on other human cancer cell types, which include nasopharyngeal carcinoma (head cancer, column 5, line 67), and glioblastoma (neuroblastoma, column 6, line 6). *Fisher* teaches that ectopic expression of mda-7 inhibits the growth of tumor cells and may provide therapeutic benefit for the treatment of human cancer (column 14, lines 62-65). Although *Fisher* did not directly administer the nucleic acid encoding MDA-7 in a human patient, they did test the MDA-7 effect on *human* cancer cells in nude mice (e.g. table 1, column 14, and figure 5). Thus, *Fisher* implicitly suggests to the skilled in the art to use

the method for treating tumor in a human patient. Given the correlation and success in the *in vitro* and *in vivo* study on human cancer cells as taught by *Fisher*, one would have had a reasonable expectation of success using such method in human patients. Thus the claimed invention was at least *prima facie* obvious over *Fisher*.

As to the underlying mechanism of action for MDA-7, *Fisher* teaches that mda-7 is a potent growth suppressing gene when over-expressed in a wide spectrum of histologically distinct human cancers (e.g. column 8, lines 41-44), and that such growth suppressing effect extends to even normal cells (col 8, lines 45-60).

Fisher does not mention that tumor is an angiogenesis-dependent disease, nor directly measures angiogenesis of the cancer. *Folkman* remedies the deficiency by establishing it was well known in the art that tumor growth are closely associated with or the cause of angiogenesis. *Folkman* teach tumor angiogeneic activity arises from the tumor cell itself in the form of the release of angiogenic molecules, and arises from host cells recruited by the tumor (e.g. the abstract). In light of such teaching, it would have been obvious to the ordinary skilled in the art that angiogenesis accompanies tumor growth, and hence suppress tumor cells would necessarily suppress tumor angiogenesis.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to recognize the method taught by *Fisher* would necessarily inhibit tumor angiogenesis when the tumor growth was suppressed, and measuring tumor volume is an indirect means for measuring tumor angiogenesis. The ordinary skilled in the art would have been motivated to apply such method in a human

cancer patient with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so as implicitly suggested by *Fisher* and because the ultimate goal of animal study is seeking for treatment strategy in humans. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 9, 18-23, 37-41, 75, 76 are newly rejected under 35 U.S.C. 103(a) as being obvious over *Fisher* (US 6,355,622), in view of *Folkman et al* (Semi in Cancer Biol 1992;3:65-71) as applied to claims 1, 4, 7, 8, 10-12, 14, 25, 33-36, 42, 43, 77-79 above, further in view of *Roth et al* (US 6,069,134), and evidenced by *Nasz et al* (Acta Microbiol Immunol Hung 2001;48(3-4):323-48).

As discussed in the immediate preceding section, *Fisher* teaches intratumoral injection of adenovirus encoding MDA-7 for treatment of cancer, and administering the vector to tumor cells *in vitro* at moi of 10^2pfu/cell, but does not specify the dosage for *in vivo* administration (column 14, line 22). *Fisher* teaches that ectopic expression of mda-7 inhibit the growth of tumor cells and may provide therapeutic benefit for the treatment of human cancer in general, but did not discuss the details of such therapy (column 14, lines 62-65), nor the combined cancer treatment regimen.

Roth et al supplemented *Fisher* by establishing that these limitations were routine in the art for treating cancer in humans. *Roth et al* detailed a method comprising administering a DNA damaging agent (e.g. cisplatin) combined with adenoviral vector expressing a tumor suppressor (e.g. p53, abstract), together with conventional

chemotherapy and surgery for the treatment of cancer (column 3, lines 20-48). *Roth et al* teach that the DNA damaging agents include gamma-irradiation, x-rays and UV-irradiation, for example; and the chemotherapeutic agents include 5-fluorouracil (column 4, lines 57-67). *Roth et al* teach that local administration was preferred method, and intravenous infusion from a site distal of tumor was contemplated (column 30, lines 40-64). *Roth et al* also teach that the adenoviral stock was administered at a m.o.i. of 10^8 pfu/ml (column 12, line 1). Moreover, *Roth et al* further evidences that the *in vitro* and mice studies of a candidate agent on human cancer cells are feasibility studies for treating a human patient, and applying such method in humans is a logical extension of the experimental studies.

Claims 20-23 and 37-41 are limitations for the timing of the combination therapy, neither *Roth et al nor Fisher* discuss the details. However, given the levels of the ordinary skilled in the art, these limitations would fall within the bounds of the optimization for a proper therapeutic regimen.

Claims 75 and 76 are drawn to the total dose of viral vectors applied to an individual ranging from 10^{10} to 10^{13}. Although *Fisher* in view of *Roth* do not teach the particular doses, it was well known in the art replication defective adenoviral vectors can be produced in very high titers (e.g. *Nasz et al*, abstract), and it was clearly within the levels of the skill to figure out a proper amount of viral vectors needed for achieving therapeutic effects.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the method as taught by *Fisher* in treating a

human subject using the regimens as taught by *Roth et al* by administering the mda-7 either prior or after the conventional therapy at a dosage sufficient for tumor cell killing with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the combined therapy would maximize the tumor-treating effect by any individual therapy alone. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

In the Remark, the applicant argues that the results in the present specification were surprising and unexpected because it was unknown that MDA-7 could inhibit angiogenesis.

In response, from the teaching of the modified rejection, it would not be surprising that mda-7 inhibits endothelial cell and angiogensis because *Fisher* teaches mda-7 is a potent growth inhibitor for tumor cells as well as normal cells (see column 8), and *Folkman* teaches the angiogenic activity of tumor arises from tumor cells, and hence when the numbers of tumor cells are reduced, so does the angiogenic activity. When combining the two factors brought by direct and indirect effects of mda-7 (inhibiting normal cell and cancer cell growth), one would have had reasonably expected a reduced angiogenesis at the site of tumor.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4, 7-12, 14, 18-23, 25, 33-43, 75-79 stand or newly provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 92-116,125-154, 159-174 of copending U.S. Patent Application No. 09/615,154, for reasons of record and set forth *supra*, particularly considering all of the limitations of cited claim 173 are taught in the instant disclosure and the cited application. Applicant is reminded that the elected species for the disease treated is angiogenesis-dependent **cancer**, and Claim 173 reads (emphasis added),

173. (Currently amended) A method for **treating a patient with cancer** comprising
1) administering to the patient by intratumoral injection an effective amount of an expression construct **comprising a nucleic acid sequence encoding a full-length human MDA-7 polypeptide** or a.[secreted] human MDA-7 polypeptide lacking the first 48 amino acids of SEQ ID NO:2 under the control era promoter operable in eukaryotic cells and
2) providing to the patient at least one other anticancer therapy, wherein the other anticancer therapy comprises a) performing surgery; b) administering chemotherapy; c) administering radiotherapy; or d) administering immunotherapy, wherein the cancer is non-small cell lung, small-cell lung, lung, hepatocarcinoma, retinoblastoma, astrocytoma, gum, tongue, neuroblastoma, head, neck, pancreatic, renal, testicular, ovarian, mesothelioma, cervical, gastrointestinal, lymphoma, brain, colon, or bladder.

In view of such, the reasoning for this rejection is self-explanatory. As to the second element of claim 173, it is encompassed by instant claims as evidenced by claims 1 and 21-23.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. JANICE LI** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30Am to 7pm Monday through Thursday, Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on 571-272-0739. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI/
Primary Examiner, Art Unit 1633

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